IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of	:	KNIPE ET AL.
Serial No	:	08/278,601
Filed	:	July 21, 1994
For	:	HERPES VIRUS REPLICATION DEFECTIVE MUTANTS
Art Unit	:	1645
Examiner	:	Caputa, A.

Assistant Commissioner for Patents
Washington, D.C. 20231

REQUEST BY APPLICANT FOR INTERFERENCE WITH PATENT PURSUANT TO 37 C.F.R.§1.607

S i r:

Under the provisions of 37 C.F.R. §1.607, applicants respectfully request that an interference be declared between the above-captioned application and U.S. Patent No.5,665,362, issued to Inglis et al.

I. Proposed Count

Applicants present the following proposed count which is identical to claim 1 of the '362 patent:

> A vaccine comprising a pharmaceutically acceptable excipient and an effective immunizing amount of a mutant herpesvirus, said mutant herpesvirus containing a genome in which a viral gene encoding a protein which is essential for production of infectious virus has been deleted or inactivated, wherein said mutant virus is able to cause production of infectious new virus particles in a recombinant complementing host cell expressing a gene which complements said essential viral gene, but is unable to cause

production of infectious new virus particles when said mutant virus infects a host cell other than said recombinant complementing host cell, for prophylactic or therapeutic use in generating an immune response in a subject infected therewith.

II. Claims 42 and 43 of Knipe

Claims 42 and 43 of Knipe are substantially copied from U.S. Patent No.5,665,362, issued to Inglis et al. Thus claims 42 and 43 are substantially identical to the proposed Count and claim 1 of the '362 patent.

Claim 42. A vaccine comprising a pharmaceutically acceptable carrier and an amount of a mutant herpesvirus effective to elicit a protective immune response, said mutant herpesvirus containing a genome in which a viral gene encoding a protein which is essential for production of infectious virus has been deleted or inactivated, wherein said mutant virus is able to cause production of infectious new virus particles in a recombinant complementing host cell expressing a gene which complements said essential viral gene, but is unable to cause production of infectious new virus particles when said mutant virus infects a host cell other than said recombinant complementing host cell, for prophylactic or therapeutic use in generating an immune response in a subject infected therewith.

Claim 43. A vaccine comprising a pharmaceutically acceptable carrier and an amount of a mutant herpesvirus effective to elicit a protective immune response, said mutant herpesvirus containing a genome in which a viral gene encoding a protein which is essential for production of virus has been deleted or inactivated, wherein said mutant virus is able to cause production of new virus particles in a recombinant complementing host cell expressing a gene which complements said essential viral gene, but is unable to cause production of new virus particles when said mutant virus infects a host cell other than said recombinant complementing host cell, for prophylactic or therapeutic use in generating an immune response in a subject infected therewith.

Knipe claim 42 is identical to claim 1 of the '362 patent, except as follows:

(i) The term "pharmaceutically acceptable carrier" (Knipe claim 42) and the term "pharmaceutically acceptable excipient" (Inglis' claim 1 and the proposed Count) are synonymous and, therefore, claim 42 corresponds to the proposed Count.

(ii) The term "an amount of mutant herpesvirus effective to elicit a protective immune response" (Knipe claim 42) and the term "an effective immunizing amount of a mutant herpesvirus" (Inglis' claim 1 and the proposed Count) are synonymous and, therefore, claim 42 corresponds to the Count. In this respect, an "immunizing amount" and a "protective amount" both denote that there is protection against herpesvirus.

In regard to Knipe claim 43, claim 43 differs from claim 42 by claim 43 defining that the mutated gene is one "essential for production of virus," whereas claim 42 and the proposed Count define that the mutated gene is one "essential for production of infectious virus."

The terminology of claim 43 in this respect encompasses the terminology of the proposed Count in that if, as defined by claim 43, there is no production of virus, there clearly is no production of infectious virus.

Claims 42 and 43 correspond to the proposed Count in that each is directed to a vaccine that employs a mutated herpesvirus to produce a protective response, wherein the mutation is one that prevents production of infectious virus, wherein the mutated virus can be generated by the use of a complementing cell line.

III. Support For Claims 42 and 43

Claim 42 is clearly supported by the specification. In particular, the specification is directed to the use of a herpesvirus in which a gene is mutated, with such gene mutation preventing further virus production in an infected cell, other than an infected cell capable of producing the protein encoded by the mutated gene. The specification discloses that such a mutated herpesvirus, in combination with a carrier, is used as a vaccine for eliciting a protective immune response.

The following are representative examples of where various portions of claim 42 is supported in the specification:

1. "a vaccine" (page 6);
2. "a pharmaceutically acceptable carrier" (p. 2, lines 28 - 29; p. 3, line 31);
3. "an amount of a mutant herpesvirus effective to elicit a protective immune response" (page 11, lines 27-32; page 2, lines 29-31; page 45, lines 1-33).
4. "said mutant herpesvirus containing a genome in which a viral gene encoding a protein which is essential for production of infectious virus has been deleted or inactivated" (page 8, lines 1-15; page 11, lines 7 and 8).
5. "wherein said mutant virus is able to cause production of infectious new virus particles in a recombinant complementing host cell expressing a gene which complements said essential viral gene, but is unable to cause production of infectious new virus particles when said mutant virus infects a host cell other than said recombinant complementing host cell". Note Page 20, lines 26-35, which states:

> "Plaque assays were performed to determine whether the mutants were capable of growth in Vero cells. All five mutants were unable to form plaques in Vero cells at the lowest dilution which could be tested. However each mutant formed plaques efficiently on V27 cells. Because the only known intact HSV-1 gene resident on the V27 genome is a wild-type copy of the ICP27 gene, these results indicate that the lethal defect in each mutant is complemented in trans by this wild-type form of ICP27."

Also note Page 34, line 27 through page 35, line 8, which states in part:

> "Each of the mutant viruses presented in Figure 12 was unable to replicate in Vero cells and required complementation by the wild-type copy of the ICP8 gene present in B10 or S2 cells. Each of the mutant viruses replicated to levels similar to wild-type levels in these ICP-38 expressing cell lines."

Further note page 46, lines 8-11, which states:

> Mutant virus such as those described above cannot replicate in cells which do not express a wild-type complementing form of the gene. They therefore cannot spread beyond the site of the initial infection.

6. "for prophylactic or therapeutic use in generating an immune response in a subject infected therewith". Note p. 45 lines14-23:

> "Control mice which had received only the wild-type virus had a survival rate of less that 20%. Reproducibly, in subsequent experiments performed with all three mutant viruses (d120, d301 and n504), while only 1/9 control (PBS injected) mice survived, preinoculation of mice with either ICP27 or ICP8 mutants resulted in 100% survival following challenge with wild-type virus. Even the ICP4 which expresses only the immediate-early genes, protected the majority of mice."

Claim 43, which is essentially identical to claim 42, is similarly supported. In particular, note that page 11, line 15 of the present specification discloses that there is no production of progeny virus.

The proposed Count is directed to a vaccine comprising a mutated herpesvirus wherein the mutation prevents production of infectious herpesvirus.

The Inglis patent discloses that the production of infectious herpesvirus may be accomplished in two different ways: mutation of a gene that prevents infection of other cells or mutation of a gene that prevents viral production. In either case, there is no production of infectious virus in that, in the latter case, there is no viral production, whereby no infectious virus is produced. In the former case, virus is produced but the virus is not infectious, whereby there is no production of infectious virus; i.e., no production of a virus that is infectious. In this respect, please note for example col. 3, lines 9-13 of Inglis.

In the present application, the genes that are mutated prevent virus production and, therefore, there is no production of infectious virus.

IV. Knipe Claim 44

Claim 44 of Knipe is substantially copied from U.S. Patent No. 5,665,362 issued to Inglis et al. Thus claim 44 is substantially identical to the proposed Count and claim 1 of the '362 patent.

> Claim 44. A vaccine comprising a pharmaceutically acceptable carrier and an amount of a mutant herpesvirus effective to elicit a protective immune response, said mutant herpesvirus containing a genome in which a viral gene encoding a protein which is essential for replication of the virus has been deleted or inactivated, wherein said mutant virus is able to cause production of new virus particles in a recombinant complementing host cell expressing a gene which complements said essential viral gene, but is unable to cause production of new virus particles when said mutant virus infects a host cell other than said recombinant complementing host cell, for prophylactic or therapeutic use in generating an immune response in a subject infected therewith

Claim 44 substantially corresponds to the count for the reasons presented above for claims 42 and 43, in that claim 44 is directed to a vaccine which includes a mutated herpesvirus wherein the mutation prevents virus replication.

Claim 44 differs from claims 42 and 43 by defining that the mutated gene is one "essential for replication of the virus", whereas claim 42 and the proposed Count define that the mutated gene is one "essential for production of infectious virus" and claim 43 defines the mutated gene as one "essential for production of virus".

The terminology of claim 44 corresponds to that of the proposed count with respect to the language "essential for replication" in that without replication of the virus, no new virus is produced. Thus if a mutant virus is replication defective, it is incapable of producing infectious virus.

In view of the fact that the proposed count is directed to a vaccine comprising a mutated herpes virus, wherein the mutation prevents infectious virus production (no infectious virus is produced), claim 44 corresponds to the count.

Although claim 44 corresponds to the proposed Count in that it is a species within the genus of the count, claim 44 is also patentable over the count in that it specifically defines that the mutation is in a gene required for replication. It could not have been reasonably predicted that such a mutated virus would be suitable for use as a vaccine in that Inglis would lead one skilled in the art to expect that mutation of an early gene would reduce immunogenicity (see Inglis col.3 lines 33-36).

Similarly, claims 42-52 both correspond to the proposed count and are patentable over the proposed count.

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